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Immunoglobulin A and the Kidney

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *The case presentation is by Mr. James Kahn.*

MR. KAHN:†The patient is a 37-year-old man who was admitted because of failing memory and progressive renal failure. He had been admitted to another hospital 17 years earlier for evaluation of hematuria associated with frequent upper respiratory tract infections. Renal biopsy was done then and was nondiagnostic, although he was told he had glomerulonephritis. A number of years later, 3½ before the present admission, his blood urea nitrogen (BUN) was noted to be 31 mg per dl and creatinine was 1.7 mg per dl. Creatinine clearance at that time was 38 ml a minute. Results of analysis of urine were significant for proteinuria (3+) and hematuria (1+). The urine sediment contained five oval fat bodies and 10 to 30 erythrocytes. Six months before admission his BUN was 54 mg and creatinine was 4.5 mg per dl. On admission, the BUN was 98 mg and creatinine was 10.5 mg per dl.

The past medical history and review of systems were noncontributory. There is a family history of hypertension but none of kidney disease.

On physical examination, his blood pressure was 180/120 mm of mercury, pulse rate 80 per minute, respirations normal and he was afebrile. Results of the physical examination were unremarkable except for a harsh grade 2/6 holosystolic murmur that was heard best at the third left intercostal space along the sternal border and did not radiate.

Laboratory studies included a urine analysis that showed 3+ hemoglobin, 1+ protein, 10 to 30 erythrocytes per high power field and one erythrocyte cast. Creatinine clearance was 18 ml a minute. He had a hematocrit of 27 percent. Findings on a roentgenogram of the chest, an electrocardiogram and an echocardiogram were all normal. An x-ray study of his abdomen showed the kidneys to be 10 cm in length. A renal biopsy was done and on light microscopy of the specimen four of seven glomeruli were seen to be completely sclerosed and three out of seven had increased cellularity of the mesangial matrix with capillary sclerosis. Immunofluorescence microscopy showed mesangial staining for immunoglobulin A, C3 and C4. Electron microscopy showed deposits of granular material in the mesangium without any membranous or endomembranous deposits. The diagnosis was IgA nephropathy. Since that time the patient has had an arteriovenous fistula placed and is being treated with hemodialysis.

DR. SMITH: *Dr. James Naughton will discuss the case.*

DR. NAUGHTON:‡ The case presented today is an example of that spectrum of diseases wherein immunoglobulin A is selectively deposited in the renal glomerulus. It is important to realize that

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TABLE 1.—*Clinical Presentations of Renal Diseases Associated With Glomerular IgA Deposition*

Diseases	*Common Syndromes*	*Rare Syndromes*
1. IgA nephropathy (Berger's disease)	Focal glomerulonephritis with macroscopic hematuria (1)*	Nephrotic syndrome (1,2,3)
2. Schönlein-Henoch purpura	Acute glomerulonephritis (2,1)	Malignant hypertension (1,2)
3. Hepatic glomerulonephritis	Chronic glomerulonephritis leading to renal failure (1,2,3)	Rapidly progressive glomerulonephritis (2,1)
	Asymptomatic urinary abnormalities (1,3)	Acute renal failure (1)

*Numbers in parentheses after each syndrome indicate the disease reported to occur with that syndrome in approximate order of frequency.

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
HLA = human leukocyte antigen
SHP = Schönlein-Henoch purpura
SLE = systemic lupus erythematosus

this case also typifies a relatively common diagnostic dilemma—that is, a patient who is first seen with far advanced renal disease but no established cause for the renal failure. More than 50 percent of all patients with kidney disease in the United States who eventually become candidates for hemodialysis or transplantation have some form of glomerulonephritis as the cause of their end-stage renal disease. In about a third of patients with glomerulonephritis, the disorder has developed as the result of one of the systemic diseases that we recognize as leading to that complication, most commonly systemic lupus erythematosus (SLE), less commonly polyarteritis nodosa, Wegener's granulomatosis, and so forth. In the remaining two thirds of patients with glomerulonephritis who end up with end-stage renal disease in the United States, the cases remain an enigma. We do not know what causes the disease in the vast majority of these patients.

The patient presented here was atypical in that, when initially seen, his kidneys were still relatively normal in size. It is more common in such a patient to find the kidneys already shrunken, which increases the risk of renal biopsy and makes a definite histologic diagnosis more difficult. Therefore, biopsy studies are not done in such a patient and dialysis or transplantation simply is carried out. Because this patient's kidneys were still normal in size and his urine sediment showed abnormal activity, there was a question as to whether he might have a treatable form of glomerulonephritis, and so he had the biopsy procedure. The histologic finding in this case is a relatively common one, as has become apparent in the last decade, though the precise prevalence of this disorder on a worldwide basis varies.

Clinical Features

I want to focus on three disorders that may appear disparate, but that seem to have a common thread of pathogenesis (Table 1). The first is so-called IgA nephropathy, which occurred in the case presented here. The eponym is Berger's disease (the French pronunciation should be retained to avoid confusion with Buerger's disease). The second disorder is Schönlein-Henoch purpura. The third is hepatic glomerulonephritis, a poorly understood condition seen in a variety of patients with end-stage liver disease.

There are four major clinical syndromes that can occur as the result of these three disorders (Table 1). The first is so-called focal glomerulonephritis with recurrent episodes of macroscopic hematuria, not unlike the initial symptoms of this patient. Seventeen years ago he described episodes of macroscopic hematuria associated with upper respiratory tract infection. That is the classic presentation of IgA nephropathy, or Berger's disease.[1]

The second syndrome is chronic glomerulonephritis leading to end-stage renal disease; the case described here also has that clinical course. Initially this was thought to be very uncommon in patients with IgA nephropathy; however, recent studies emphasizing longer periods of follow-up show this outcome more frequently, perhaps in more than 25 percent of cases.[2] The finding of hypertension or significant proteinuria (or both) appears to be predictive of the subsequent loss of renal function.

The third presentation is that of acute glomerulonephritis with the classic features of edema, proteinuria and hypertension. This occurs most commonly with Schönlein-Henoch purpura in children.

The final presentation would be that of asymptomatic microscopic hematuria and mild degrees of proteinuria (generally less than a gram a day).

That characterizes the third group of patients, those with hepatic glomerulonephritis, and also is frequently seen in patients with Berger's disease during the intervals between episodes of macroscopic hematuria. Other syndromes may occur, including nephrosis, malignant hypertension and acute renal failure, but they are uncommon.[3-5]

We will now look at the three diseases in more detail. In 1968 Berger and Hinglais[1] reported on a series of 55 patients, children and adults, who had recurrent episodes of macroscopic hematuria following upper respiratory tract infections. The histologic features that they described in those patients are as follows. On light microscopy there is hypercellularity in the mesangial cells of the glomerulus, whereas the remaining glomerular cells appear normal. The mesangial cell hyperplasia may be apparent in only some glomeruli and not in others, giving rise to the term focal glomerulonephritis. On immunofluorescent staining, the areas of mesangial cell proliferation characteristically stain with anti-IgA, but the glomerular capillaries themselves do not stain for IgA. Variable amounts of IgA, C3 and properdin are also commonly seen. Finally, on electron microscopy one sees electron-dense deposits in the mesangial cells that correspond to the IgA-staining particles on immunofluorescence. The mesangial cell surface comes in contact with blood circulating through the glomerulus in an area where the capillary basement membrane is discontinuous. Apparently these cells possess phagocytic activity and will engulf particles that are otherwise too large to pass through the basement membrane, giving rise to mesangial forms of glomerulonephritis. In the disorders I will review here, the particles that find their way into the mesangial cells contain IgA.

IgA Nephropathy

The clinical features of IgA nephropathy can be summarized as follows: There is a pronounced male predominance with a sex ratio of about 4:1 or 5:1. It is a disease of young adults with the peak ages of onset between 16 and 35. Typically, the episodes of gross hematuria occur after respiratory and gastrointestinal tract infections, and the onset of the episodes of hematuria is within 24 to 48 hours of onset of the clinical symptoms of the upper respiratory tract infection or the gastroenteritis. This would be in contrast to poststreptococcal glomerulonephritis, which has a latent period of 10 to 14 days after streptococcal infection before hematuria appears. Patients with IgA nephropathy have hematuria at the peak of their clinical symptoms.

The prevalence on a worldwide basis is variable. Recent reports from France, Japan and Australia indicate that among patients studied for primary glomerular disease, IgA nephropathy accounts for 20 percent to 25 percent of all cases.[6-8] In a recent series from Australia, IgA nephropathy was found in 12 percent of all renal biopsy specimens, making it the single most common histopathologic finding in renal biopsies in Australia.[6] IgA nephropathy appears to be less frequent in the United States, being found in about 5 percent of all biopsy specimens[9] and occurring in perhaps 10 percent to 15 percent of primary glomerular diseases. On laboratory examination, the most common findings are increased levels of serum IgA, which are present in more than half of the patients,[3,8] particularly when the IgA levels are measured at the time of a clinical flare of the disease. Some normal laboratory findings are important: serum complement levels are typically in the normal range, and tests for circulating immune complexes usually give normal findings. There has been a familial trend in some reports wherein several family members have had IgA nephropathy, raising the possibility of a genetic determinant. There are scattered reports from different parts of the world of human leukocyte antigen (HLA) associations, HLA-B35 in one series[10] and HLA-A12 in another,[11] whereas others have reported a lack of HLA association.[3,12] These variable associations probably reflect linkage disequilibrium of A or B loci in certain ethnic groups. For example, in a series of patients from Japan one might find a certain HLA association, but when another investigator examines a European population, that linkage is not present and no association is found.

HLA typing of the D locus has not been carried out in a large series of patients with IgA nephropathy. A recently published letter from France[13] reported that more than half of the patients who present with IgA nephropathy have loci typed at HLA-Dw4. This is the same locus that appears with increased frequency in rheumatoid arthritis and in a variety of other diseases. Although this is only a preliminary communication and it has not been confirmed elsewhere, it is interesting to relate the possibility of HLA-Dw4 association to some of the clinical findings reported in patients with IgA nephropathy. For instance, a Japanese study reports that in 6 of 39 patients with IgA

nephropathy followed for three years scleritis developed.[14] Scleritis, of course, is a well-described complication seen in patients with rheumatoid arthritis. Other clinical associations reported with IgA nephropathy include cyclic neutropenia, mycosis fungoides,[15] dermatitis herpetiformis[16] and asymptomatic pulmonary hemosiderosis[17]; these are primarily isolated case reports.

Schönlein-Henoch Purpura

Description of the second group of disorders, Schönlein-Henoch purpura (SHP), is historically much older. Berger's disease was first described in 1968.[1] If we look carefully at the history of SHP, we will find that it was probably first described in 1808.[18] As is often the case with eponymic diseases, history shows that the person for whom the disease was named has a tenuous claim to that honor. The first two people to describe this disorder—that is, to describe an association of abdominal pain and purpura—were Heberden and Willen in independent reports in 1808. In 1837 Schönlein added arthritis as a third component to the triad of purpuric rash and abdominal pain. It was not until the 1870's that Henoch enters the picture, when he added the presence of gastrointestinal hemorrhage and later that of hematuria to complete the syndrome.

The common clinical findings include a nonthrombocytopenic vasculitic purpuric rash, characteristically found over the lower extremities and the buttocks. There is an old clinical pearl in pediatrics that when a child has acute abdominal pain, one must always look at the skin on the legs and the buttocks for the rash of SHP; children have undergone exploratory laparotomy that may have been avoided by noting the presence of this rash. Arthralgias, abdominal pain, gastrointestinal bleeding and hematuria are the other common features seen in both children and adults, though the disorder is much more common in children. Skin involvement, which is the sine qua non of the disorder, is present in 100 percent of cases, with purpura being vastly the most common lesion seen, though a maculopapular rash also occurs. Children may have local cutaneous edema, particularly very young children. This observation is credited to Osler, who emphasized some of the allergic features of the disease, leading to the term "anaphylactoid purpura" as another name for SHP.

Joint symptoms and hematuria are common in adults. The gastrointestinal features, both pain and bleeding, are less common in adults than in children. SHP has a generally good prognosis. Many patients will have a relapsing course; that is, the disease will flare repeatedly, usually after upper respiratory tract infections, and then over a period of years it fades away. Some patients are left with renal impairment. It would appear that roughly 20 percent of adults who have an episode of SHP will be left with mild hypertension or persistent urinary abnormalities, or both, and then in a smaller percentage of those patients, end-stage renal disease will develop. In the pediatric population, about 15 percent of all children who ultimately require dialysis or transplantation have SHP as the cause of their renal failure.[19] That is a far higher percentage than would be seen in the adult population. The histology of this lesion is essentially identical to that of Berger's disease, predominantly mesangial cell hyperplasia with mesangial deposition of IgA-containing immune complexes.

Hepatic Glomerulonephritis

It has been observed over the last decade that patients with a variety of end-stage liver diseases commonly show asymptomatic urinary abnormalities on careful analysis of the urine, chiefly hematuria and proteinuria. Histologic examination of the kidney in these patients, usually done at autopsy, shows the same pathologic features seen in IgA nephropathy and SHP: mesangial deposition of IgA.[5,20] The prevalence of this finding in patients with advanced liver disease is unknown. In the few series that have reported studies of immunofluorescent staining of renal tissue in all patients dying with end-stage liver disease, this histologic picture was seen in more than half the patients studied.[20] These reports are primarily from Europe, as this has not been an area of much interest in the United States. Generally these patients are asymptomatic, renal failure rarely develops as a consequence of this mechanism and, unlike in both SHP and IgA nephropathy, you do not see an association with upper respiratory or gastrointestinal tract infections and flares of the renal disease.

Pathogenesis

The pathogenesis of these disorders is not well understood, but there are four general areas that I will address (Table 2):

TABLE 2.—*Pathogenesis of Renal IgA Disorders*

Immune Complexes (IC)
Circulating IC not detected by Raji cell, Clq binding or conglutinin assays
IC may be detected by anti-IgA assay
Complement
Serum levels usually normal
Variable amounts of C3, properdin and, less commonly, C4 are seen in renal mesangium
Animal model does not need complement to produce the renal lesion
Source of the IgA
No secretory piece or J piece can be routinely shown in renal IgA
Studies on IgA1 vs IgA2 in renal tissue have been conflicting, but probably predominantly IgA1 is deposited
Most evidence currently favors IgA derived from marrow rather than from mucosal sources

- What is the role of circulating immune complexes?
- What is the role of complement?
- Where does the IgA come from?
- Are there pathogenic interrelationships among these three disorders?

Immune Complexes

IgA-containing complexes are seen in the mesangial cells in all three disorders. The standard tests for circulating immune complexes, including the Raji cell, the Clq binding assay and the conglutinin assay, are usually negative in patients with IgA nephropathy and SHP.[21] Recent reports suggest that immune complexes can be detected in these patients by using an anti-IgA assay.[22] Whether they are detecting true immune complexes (that is, combinations of IgA and an antigen) or whether they are detecting aggregates of IgA (polymeric IgA) remains to be determined. Serum IgA levels are elevated in most of these patients and polymeric (aggregates of the smaller 7S molecules) IgA levels are also elevated. It is also possible that the immune complexes are formed in the mesangial cells by the separate trapping of circulating antigen and antibody.

Complement

Serum complement levels are classically normal in these disorders.[3] This can be helpful in excluding poststreptococcal glomerulonephritis in a patient who has hematuria after an upper respiratory tract infection because patients with poststreptococcal glomerulonephritis are hypocomplementemic. However, immunofluorescence staining commonly shows the presence of C3 and properdin in mesangial cells, but usually not the early reacting complement components, C4 and Clq. This suggests that activation of the alternate pathway of complement may be important in the pathogenesis.

There is now an animal model for IgA nephropathy.[24] It uses an IgA-producing myeloma cell line in mice. The IgA is incubated with dinitrophenol-treated bovine serum albumin, producing an IgA complex that will in turn induce hematuria and the histologic features of IgA nephropathy in mice. There are two important observations from studies in mice: First, the lesion can be induced only by using polymeric IgA. If individual 7S IgA is used, no lesion is produced. Second, if the mice are first depleted of complement by using snake venom and the IgA complexes then administered, the same histologic lesion will develop. This would suggest that complement is not necessary for the pathogenesis of the lesion. This is also consistent with the absence of inflammatory changes that should be seen when there is complement activation; that is, in neither human patients nor in mice is there migration of polymorphonuclear leukocytes into the glomerulus or endocapillary proliferation.

Where Does the IgA Come From?

It is intriguing to speculate that because SHP and IgA nephropathy appear after respiratory and gastrointestinal tract infections, perhaps IgA responses at mucosal barriers are important in pathogenesis. We recognize two kinds of IgA in humans, that which circulates in blood and that found in mucosal secretions. In blood, IgA is present in about one fifth the concentration of IgG, whereas in mucosal secretions IgA represents more than half of all immunoglobulin present in those secretions.

Secretory IgA is derived from a population of plasma cells that exist in the submucosa along the respiratory, gastrointestinal and genitourinary tracts. These plasma cells elaborate a dimer of IgA molecules that are hooked together by a so-called J chain, which also is derived from plasma cells. That is the form in which the immunoglobulin is secreted from the plasma cell into the submucosal space. A product is then elaborated by the mucosal cell itself, a nonimmunoglobulin glycoprotein called secretory component. A secretory

component attaches to the dimer of IgA and enables it to be transported out into the lumen of the mucosal tissue. Therefore, there are several characteristics that would enable one to distinguish secretory IgA from the IgA that is derived from bone marrow plasma cells.

A final observation is that independent of the presence of the J chain, the dimer and the secretory piece, there is another distinguishing feature among all IgA molecules. IgA is classified further as IgA1 and IgA2 based on whether or not the molecule is cleaved by IgA protease. Certain bacteria—for example, pathogenic strains of *Neisseria*—elaborate a proteolytic enzyme that inactivates IgA by breaking the molecule in one area of the heavy chain. IgA1 is inactivated by IgA protease, IgA2 is resistant to IgA protease. Secretions of the respiratory and gastrointestinal tracts contain 50 percent to 60 percent IgA2. This is thought to have evolved because of the selective advantage of elaborating a molecule that is resistant to the IgA protease. The IgA that circulates in blood, however, is only about 10 percent IgA2; the remainder is the protease-sensitive form.

To summarize the data at this point in patients with IgA renal diseases, we have the following observations. If you examine the IgA deposited in the glomerulus there is no secretory piece demonstrable[25]; similarly, J piece is usually not found. These two observations would argue that there is no evidence that the IgA present in the kidney is derived from mucosal secretions. There is conflicting evidence as to whether the IgA in kidney is IgA1 or IgA2. A disproportionate amount of IgA2 in the kidney would argue for a secretory origin. Unfortunately there are two recent papers on this issue that are completely conflicting.[26,27] André and co-workers[26] reported on groups of patients with IgA nephropathy, SHP and hepatic glomerulonephritis and a few patients with SLE who had glomerular deposition of IgA. By their methods they found more IgA2 in the patients with IgA nephropathy, SHP and liver disease, whereas the SLE patients had predominantly IgA1. They concluded that the IgA in the first three disorders was of mucosal origin. At the same time, Conley and colleagues[27] published exactly the opposite results. Using different reagents they found primarily IgA1 in patients with IgA nephropathy and SHP. There has subsequently been a letter published that supports the results of Conley and associates and not André and coworkers' results. In summary, at this time there is no conclusive evidence of a mucosal source for the IgA, despite the relation between respiratory and gastrointestinal tract infections and flares of the renal disease.

TABLE 3.—*Relation of All IgA Nephropathies*

All three disorders are immunohistologically identical
Extrarenal IgA deposition (especially skin) is seen in Berger's disease and Schönlein-Henoch purpura
Serum IgA levels are usually elevated in all three disorders
Polymeric IgA is necessary to create lesions in animal model; a normal liver clears polymeric IgA from the circulation

TABLE 4.—*Approach to Diagnosis*

Analysis of urine to include examination of erythrocyte morphology by phase contrast microscopy
Measure serum IgA level
Take a biopsy of normal skin to determine deposition of capillary IgA
Renal biopsy if renal function impaired or if protein reaction in urine is greater than 1.0 grams/24 hr.

Pathogenic Relationships

Are there pathogenic relationships among these disorders? All three of the diseases have the same morphology (Table 3). That is, IgA nephropathy, SHP and hepatic glomerulonephritis are largely indistinguishable on studies of renal biopsy specimens. In IgA nephropathy and certainly in SHP it is now clear that extrarenal deposits of IgA are very common and are typically seen in skin biopsy specimens.[28] We do not have comparable information on the patients with hepatic glomerulonephritis. Again, there is no apparent association between mucosal infections and renal disease in hepatic glomerulonephritis. The liver disease is therefore somewhat different from the other two disorders. The common pathogenic link to liver disease may be as follows: It appears that normal liver has a specific transport process for picking up polymeric IgA and transporting it from plasma into the biliary tract. It is not clear how much of the IgA in gastrointestinal secretions is derived from that mechanism, but it appears to be significant and is easily seen in experimental animals. If experimental liver disease is induced in a rat by mechanisms as diverse as carbon tetrachloride poisoning or by ligating the common bile duct, there is an immediate increase in circulating IgA, chiefly of the polymeric fraction.[29] Patients with hepatic glomerulonephritis also have elevated circulating IgA levels, again of the polymeric frac-

tion. In advanced liver disease, therefore, the decreased clearance of polymeric IgA may predispose to renal deposition. As stated before, in the mouse model of IgA nephropathy only polymeric IgA would induce renal disease.

Diagnosis

Turning now from the subject of pathogenesis, I will review the diagnostic approach to these disorders (Table 4), emphasizing the use of urine analysis, skin biopsy and renal biopsy. I have already mentioned that serum IgA levels are often elevated in these disorders and, therefore, measuring IgA levels can be an important diagnostic tool. With urine analysis, we are classically taught that when a patient has hematuria, one would suspect a glomerular origin only when either erythrocyte casts are seen, or significant proteinuria is present, or both. In the absence of those two findings, we are taught to pursue a structural evaluation of the urinary tract—cystoscopy, intravenous pyelography and perhaps even arteriography. Recent reports from Australia suggest that simply by examining the morphology of erythrocytes in fresh urine under phase contrast microscopy one can readily distinguish between glomerular and nonglomerular hematuria.[30] Erythrocytes of glomerular origin appear prominently dysmorphic with variations in size, fragmentation and a peculiar form that has the appearance of budding yeast. Erythrocytes of nonglomerular origin are much more regular, occurring as either normal biconcave cells or ghost forms. Fairley and Birch[30] reported on 88 patients who were referred to the Royal Melbourne Hospital for evaluation of hematuria. The ultimate diagnosis was confirmed by renal biopsy and by full urinary tract evaluation in all cases. Of the 88 patients, 58 proved to have glomerular disease by biopsy, and 30 had nonglomerular disease with the usual array of stones, tumors and so forth. This simple technique of analysis of the urine identified virtually all of the patients in both groups. Of the 58 patients with glomerular disease, 55 had completely dysmorphic erythrocytes, whereas 3 of the 58 cases had a mixture of about 80 percent dysmorphic and 20 percent normal erythrocytes. Interestingly, all three of those cases turned out to have IgA nephropathy. None of the 30 cases of nonglomerular hematuria had dysmorphic erythrocytes, however. Although this observation has not been confirmed in the United States, it would appear that a simple modification of the technique of routine urine analysis would enable us to identify patients with glomerular hematuria and completely redirect our work-up at that point as to whether structural lesions or primary renal disease need be pursued. We have begun to use this technique on the renal service at the University of California, San Francisco, and are encouraged by our initial results.

We will next consider the skin biopsy. As mentioned earlier, there are several series now that have shown that patients with SHP and IgA nephropathy commonly have extrarenal deposits of IgA. This has been most carefully examined in a large series reported from Belgium[28] wherein 262 patients with a variety of renal diseases all had skin biopsies. Biopsy specimens were taken of clinically normal skin from the volar aspect of the forearm (biopsies were not done of rashes). Of the 262 patients, 45 had IgA deposition in the skin, and when these results were correlated with the clinical findings, 12 of the patients were found to have SHP, of the remaining 33 patients all but one had IgA nephropathy. The one false-positive result occurred in a case of acute tubular necrosis. There were only three patients in that series in whom results of skin biopsies were negative for IgA, but who had IgA deposition in the kidney and clinical features of IgA nephropathy. This observation is confirmed now by other studies,[3] so that it currently appears that about 90 percent of patients with Berger's disease will have positive findings on skin biopsy.

Anecdotally, our own experience has been somewhat more ambiguous. We have done a few skin biopsies on patients who had histologically confirmed IgA nephropathy but in whom IgA deposition was not found. It is not clear whether results of skin biopsies are more likely to be positive when the disease is active. I think at this point, when confronted with a patient with the appropriate history, recurrent episodes of macroscopic hematuria and dysmorphic erythrocytes on analysis of urine, one should both measure serum IgA levels and do a skin biopsy. If IgA is seen in the skin capillaries and serum levels are elevated, a presumptive diagnosis of IgA nephropathy is then established and one need not pursue it beyond that point.

What about a patient in whom the results of a skin biopsy are negative? How far do you go in this evaluation? I would suggest that if a patient's renal function deteriorates, as determined by a creatinine clearance exceeding 1,000 mg in a 24-hour collection, or significant proteinuria de-

velops, or both, that patient might well be considered for renal biopsy to establish the cause of the disease and to find out whether it is treatable. In the absence of those findings, I think it is safe to simply observe these patients.

Treatment

We can say there is no treatment at this time, which is true. However, a few comments are worth making. There is some evidence in the literature that patients with acute episodes of SHP will have lessening of their abdominal pain and joint symptoms with brief courses of corticosteroids.[18] Corticosteroids and immunosuppressive drug therapy, however, have not been shown to influence the course of renal disease in either SHP[19] or Berger's disease.[3] The most imaginative therapeutic trials to date have come from both Australia and Europe, where a series of patients have been treated with diphenylhydantoin.[3] It was observed more than a decade ago that in many patients treated with this anticonvulsant for the usual clinical indications, levels of circulating IgA fell.[31] In fact, clinically evident IgA deficiency has even been described as a complication of diphenylhydantoin treatment. This led Clarkson and associates[3] to begin administering this drug prospectively in a randomized, controlled study to groups of patients with IgA nephropathy. Unfortunately, the results to this point do not suggest any significant effect on the course of renal function. They have reported that clinical episodes of macroscopic hematuria are decreased in the patients treated with diphenylhydantoin, but otherwise the progression of their renal disease seems to be unaffected. Most patients so treated do have return of their IgA levels to normal. In patients in whom end-stage renal disease develops from IgA nephropathy, histologic recurrence of the disease has been reported following renal transplantation.[7] However, graft failure on the basis of recurrent disease rarely occurs (the first such case has recently been seen on the University of California, San Francisco, transplant service) and the presence of IgA nephropathy should not be considered a contraindication to transplantation.

Summary

We have looked at three diseases that are morphologically similar yet may have diverse clinical features. Within this spectrum of disease, the one that is the most common and most likely to be encountered by internists is IgA nephropathy. There are now several relatively noninvasive techniques that can lead to the diagnosis. Effective treatment is not yet available and, although the clinical course in many of these patients will be benign, progressive renal failure will develop in others.

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